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American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents — Back Numbers, 50 Cents

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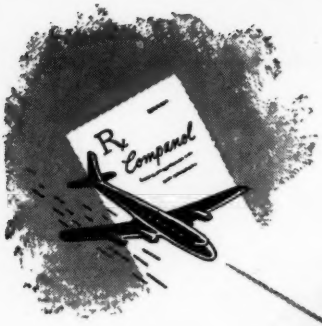

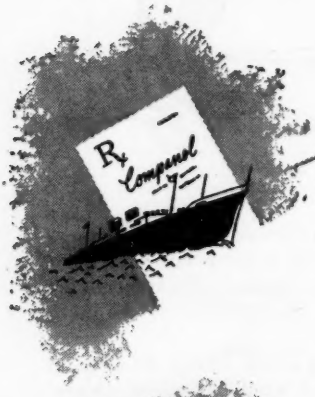

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Vol. 119. JULY 1947 No. 7

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E D I T O R I A L

INACCURACY IN PRESCRIPTIONS.

STUDIES conducted in two different states by food and drug officials have shown that an alarming situation prevails in the ranks of retail pharmacy. Simple prescriptions requiring weighing and measuring were filled in such a careless manner that the deviation from the specified strengths was as much as 68 per cent and in many cases 20 to 30 per cent. Only a comparatively few pharmacists filled the prescriptions submitted to them with the accuracy which the public has a right to expect.

In reporting one of these surveys Vincent E. Stewart writes in the *Quarterly Bulletin of Food & Drug Officials of the United States* as follows:

> . . . "What accounts for the inaccuracy which we have observed? Perhaps it is inadequate training by the colleges and universities. However, it is my opinion that this is not the reason. Surely the fledgeling pharmacist would have failed both his college course and the State Board exam if he was unable to compound the simple prescriptions which we have used in this survey.
>
> The true cause of inaccuracy seems to be the druggist's present role as manager of a department store. In most drug stores the compounding of prescriptions occupies only a minor portion of the druggist's time. Even when he does finally compound a prescription the job is sandwiched in between a dozen other tasks, usually done hurriedly, and is not given the proper consideration which is necessary for reasonably precise work. The druggist of today is primarily a merchant. His chief interest is his business and the compounding of prescriptions is a minor side-line.
>
> Another cause of inaccuracy is the illegibility of prescriptions. In our survey special care was taken to insure against any question as to what was intended in the prescription. Yet a large portion of the prescriptions which are received by drug-

gists are so nearly illegible that it is only familiarity with the physician's writing that enables them to hazard a guess as to the intent.

The present trend is toward a decrease in the compounding of prescriptions by druggists. Already a considerable portion of the so-called prescription work consists merely in removing the manufacturer's label and substituting a prescription label. Perhaps it is fortunate that the trend is such. Drugs prepared by the huge pharmaceutical houses in large lots are checked and re-checked, and careful control analyses are made on each lot. In addition, these are frequently analyzed by the State and Federal laboratories. Disastrous mistakes have been made in these preparations, and inaccuracies still occur. Still their batting average is considerably better than that of individually compounded prescriptions. If this trend continues the compounding of prescriptions in the apothecary's shop will become a lost art."

This is indeed a serious accusation and one which pharmacists must face and face honestly. We as pharmacists are trusted implicitly by the public to fill safely and accurately the prescriptions written by physicians. To do this is our professional obligation as it has been since the earliest days of pharmacy. Nothing could or will more quickly destroy public confidence in us than these proven departures from professional skill and integrity.

This matter is of such importance that it cannot be left to the discretion of individual pharmacists to mend their professional ways. Pharmacy through its own organizations, state boards and state associations, should immediately warn all pharmacists in each state of the seriousness of the situation and the likely consequences if it is not remedied. In addition, some system of self-policing should be instituted. We cannot permit other groups to point out our weaknesses and take action to correct them. This we must do ourselves. State Boards of Pharmacy might well place in operation a system of checks on prescription accuracy and suspend, temporarily at least, those who do not perform their professional work with a reasonable degree of accuracy. In many places, such as England, pharmaceutical organizations do just this and the result is a much greater regard for professional conduct.

Failure on the part of pharmacy to police itself and to do so efficiently will soon lead to others doing it for us and with such a fanfare of publicity that our respected place as one of the health professions may be lost. The impact on the medical profession will also be of harmful proportions if our arguments in favor of prescription writing are so easily refuted by the accusation of inaccuracy and inefficiency which is either condoned by organized pharmacy or tolerated by a spirit of *"laissez-faire."*

This is indeed a problem demanding attention and forthright action.

L. F. Tice.

TESTING (IN VIVO) OF DISINFECTANTS
(Using Iodine Tinctures and Solutions as Antiseptics)

By Louis Gershenfeld and Jack C. Miller *

Introduction and History

THE testing, evaluation and standardization of disinfectants have attracted much attention. There is as yet no available *in vitro* test which can be regarded as the one best suited for evaluating the efficiency of all antiseptics and germicides.

Brewer in 1939 (1) reviewed much of the work which dealt with the methods of testing germicidal compounds. These methods are mainly *in vitro* techniques. However, bacteriostasis is often responsible for false interpretations in such tests, and, as Brewer has pointed out, "it is probable that much confusion would have been avoided if the phenol coefficient test had never been suggested in testing certain compounds."

The subject of testing skin disinfectants has been particularly important. Existing *in vitro* tests are of indirect value for comparative purposes. In lieu of this, several *in vivo* tests (2) (3) (4) (5) have been suggested which may be more comparable to actual practical conditions.

"The Infection-Prevention Test for the evaluation of skin disinfectants," suggested by Nungester and Kempf (6), has been proposed. In presenting this procedure they emphasized two principles: first, the action of the disinfectant on skin itself; and secondly, the effectiveness of the disinfectant in terms of prevention of infection in animals, not inhibition of growth in media. Since viable test organisms usually kill mice in a fairly uniform manner, survival of animal does indicate the prevention of infection. This should be more of a practical indication of disinfection than lack of growth in the test tube.

Purpose

It is the purpose of this study to present a direct *in vivo* method, a modification of the Nungester-Kempf technic, for the evaluation of skin disinfectants.

* Department of Bacteriology, Philadelphia College of Pharmacy and Science.

Method

The general technic was as follows: 30 Gm. albino swiss mice were employed which had been acclimated seven days before use.

The following steps are compared to the original Nungester-Kempf technic:

Procedure used in this study	Nungester-Kempf procedure
1. The mice were anesthetized with sodium pentobarbital (intraperitoneal injection).	1. Identical.
2. Hair was removed from the abdomen by the use of a depilatory.	2. Hair was removed from the abdomen with an electric clipper.
3. The tails of the mice were placed in 70% alcohol for 1 min. The excess alcohol was removed by swabbing with sterile cotton and the tail permitted to dry for five minutes.	3. This step was omitted.
4. The tail was contaminated by dipping into 24 hour culture of a test organism for 1 min.	4. The tail was contaminated by application with a swab which had been moistened with a broth culture of the test organism. The age of the culture was not indicated.
5. The tail was treated with antiseptic for 2 minutes by dipping the tail in a sterile tube containing the antiseptic under test.	5. Identical.
6. A ½" portion of the tail was removed and implanted in the peritoneum.	6. Identical.
7. The mice were observed daily for seven days.	7. Identical.

The tail was employed because it was believed to be the most suitable area of skin possessing the following advantages:

1. The area contaminated by the culture was constant.
2. The size of the tissue introduced into the peritoneum would be constant and better controlled.
3. A smaller incision was required.

Anesthetic: The mice were injected intraperitoneally with sodium pentobarbital (1.5 grains dissolved in 1.5 cc. of sterile isotonic solution of sodium chloride). The dosage was 3.2 mg. per 30 Gm. mouse.

Removal of Hair: The removal of the hair from the abdomen was accomplished by using a depilatory paste (barium sulfide). After a four minute contact period, the paste was removed with distilled water. This area was swabbed with sterile distilled water, dried with sterile cotton, and then swabbed with the antiseptic under test. A sterile 1" by 1" gauze was placed over this area until surgery.

Contamination of the Skin: Each anesthetized test animal was fastened to an animal board. The tail was treated with alcohol, dried and dipped into a 24 hour culture of the test organism for a 1 minute period. The test organisms used were Streptococcus NY-5 and Pneumococcus No. 2 grown in brain-veal infusion broth. However, in using the Pneumococcus No. 2 organism difficulties were encountered because of variation in temperature of the animal room during its use, and also, the unsuitability of being unable to maintain a constant virulent organism. Due to this finding, no results are reported concerning the use of this test organism, Pneumococcus No. 2.

Disinfection of the Contaminated Skin: The contaminated area of the tail was dipped into a test tube containing a solution of the antiseptic under test and permitted to remain in contact for a constant period of time (2 minutes). At the end of this period, a ½" section of the tail was removed.

Intraperitoneal Implantation of Treated Tail: An aseptic technic was employed throughout the experiment. With a five-pointed scissors a five mm. incision was made through the skin at the midline of the anesthetized and surgically prepared mouse. Another incision of approximately the same length was made through the peritoneum and muscle fascia. After cutting the tail, the piece removed was placed in the peritoneal cavity and the incision was closed and sutured with a No. 60 cotton thread.

Recovery of Bacteria: Starting from the time of implantation of the tail, the animals were observed for seven days. A routine autopsy procedure was used in streaking heart blood on a blood agar plate when mice were found dead, to determine the causative agent.

Results

Using Streptococcus NY-5:

Number mice used	Disinfectant used	Mortality rate	Operative control 2 mice used	Test organism control 5 mice used
25	Iodine Solution (2%)	0	all lived	60% mortality
25	Strong Iodine Solution (5%)	0	all lived	80% mortality
25	Iodine Tincture (2%)	0	all lived	80% mortality
25	Strong Iodine Tincture ((7%)	0	all lived	60% mortality

Control animals survived in all cases when an untreated section of the tail was introduced into the peritoneum in routine procedure.

Minimum lethal dosage of iodine tinctures and solutions was determined on a series of mice by giving intraperitoneal injections.

Iodine Solution (2%) .....133 mg./Kg.
Iodine Tincture (2%) .....133 mg./Kg.

Discussion

If it were not for the impracticability involved, clinical evalua- of antiseptics would be the most direct and desirable procedure. However, there are advantages in an animal test, employing skin contaminated with a virulent organism which can be implanted in the peritoneum of a test animal.

In the technic of Nungester and Kempf and our modification, the disinfectant is applied to the contaminated skin and its action is tested by its ability to prevent infection. It is reasonable to assume that bacteriostasis does not enter into the picture in the technic, because bacteria which cause infection are those which invade deep tissue and not the skin surface. Bacteriostatic action is reduced to a minimum by tissue fluids and circulatory blood.

On the other hand, this test has its disadvantages due to the difficulty in maintaining a constant virulent strain of the test organism, as was found especially to be the case with Pneumococcus No. 2. However, Streptococcus NY-5 was used as our test organism because it gave more consistent results and displayed other desirable properties when using this modification of the Nungester and Kempf technic.

Also, the results obtained from this method of testing disinfectants are rather meaningless if large numbers of animals are not employed. It is important to employ many mice in order to be sure that the interpretations of the results are accurate and not misleading. Constant temperature of the animal during the period of the test is an important factor. Many erroneous results were found to be produced if this condition was not carefully controlled.

Summary

A skin disinfectant evaluation test is presented which is based upon the ability of an antiseptic (iodine tinctures and solutions) applied to skin contaminated with a virulent test organism. (Streptococcus NY-5) to prevent infection where this skin is implanted in the peritoneal cavity of a mouse. The technic is a modification of the Nungester and Kempf procedure.

Using Streptococcus NY-5 as our test organism, 25 mice were employed for each disinfectant in the technic outlined above. The disinfectants employed were: Iodine Solution (2%), Strong Iodine Solution (5%), Iodine Tincture (2%), and Strong Iodine Tincture (7%). All animals survived using this procedure. There was a total average of 70% mortality in mice treated with the test organism as a control.

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A PHYTOCHEMICAL STUDY OF SANSEVIERIA ZEYLANICA

By Stanley Scheindlin, M. Sc.,* and Austin A. Dodge, Ph. D.

IN the tropics, many species of *Sansevieria* have long been esteemed for their fibers, which the natives have used for bowstrings and other purposes (1). *Sansevieria zeylanica* Willd. (Fam. *Liliaceae*), which grows in India, has been mentioned in Sanskrit literature. Its fibers were used in the bowstrings and girdles of the Hindu warrior caste (2). Of the many *Sansevieria* species, only two are reported to have been used medicinally. No pharmacological studies and few chemical studies of these species have been reported. What little work has been done on their chemistry has been superficial and inconclusive.

Sansevieria zeylanica has long been prescribed by native physicians in India. According to Dymock, Warden, and Hooper (2) it has been used as a remedy for heat of blood, gonorrhea, heart disease, itch, leprosy, fever, rheumatism, glandular enlargements, and other ailments. These authors quote Ainslie as writing that the root of *S. zeylanica* has been used in coughs and tuberculosis, and that the juice of the tender shoots has been administered to children as an expectorant. In a previous work, Dymock (3) states that the juice of the root and leaves has been used to counteract the bite of the Ghannas snake (*Daboia Russellii*).

Dymock, Warden, and Hooper (2) investigated the fresh roots of *S. zeylanica*. They diluted an alcoholic extract with acidulated water and extracted the mixture with petroleum ether and ether. After making the hydro-alcoholic mixture alkaline, they again extracted it with ether. From the petroleum ether extract they isolated a wax; from the acid ether extract they isolated salicylic acid, a neutral resin, an acid resin, a white neutral principle, and a trace of alkaloid. The alkaline ether extract yielded a crystalline alkaloid

* Submitted in partial fulfillment of requirements leading to the Master's Degree and supported by Lederle Laboratories Division American Cyanamid Company.

which they named *sansevierine*. A few color reactions of the alkaloid are given, but its melting point and other significant data are not reported.

In 1935 Chopra and Ghosh (4) repeated the isolation of sansevierine from *S. zeylanica*. They assayed the plant both by U. S. P. and B. P. methods and found only 0.018% of total alkaloids. Based on the low alkaloid content they state that "the drug could not possess any marked degree of therapeutic activity". In the absence of any pharmacological data, this conclusion does not seem at all warranted.

During the Boer War, attention was drawn to the use of *Sansevieria thyrsiflora* Thunbg. in South Africa. According to Davis (5) the Kaffirs used a decoction of the root as a vermifuge and the Boers chewed the rhizome as a remedy for piles. Davis found in the rhizome a globulin, an albumen, and a glycoside. He states that the glycoside resembles, and is perhaps identical with, glycyrrhizin. The glycoside, C_{44} H_{63} NO_{18}, was optically inactive. Different samples varied in melting point between 178° and 200°. Davis also found indications of the presence of another important constituent, but there is no record of further study in this direction.

Oliver (6) examined the juice of the fresh rhizome of *S. thyrsiflora,* confining his work to some organoleptic observations and a few chemical tests. By extracting the juice with anhydrous ether he obtained a fatty substance having the color and odor of palm oil.

In an extensive search for cardio-active drugs, P. Jaretzky (7) tested the action of the rhizome of *Sansevieria Kirkii* Bak. on the heart of frogs. It possessed only weak activity compared to that of others of the drugs studied. Jaretzky does not comment on the drug beyond listing it in a chart.

The cells connecting the fibers of *Sansevieria* plants are stated to contain valuable colloidal gelling constituents, processes for the extraction of which have been patented in England (8, 9). These processes are applicable to tissues of sisal and related plants such as *Sansevieria,* American aloe, and Henequen. The residues or pulp remaining after mechanical separation of the fibers from the leaves, are extracted with an aqueous solution of tri-sodium phosphate (8) or of sodium hexametaphosphate.(9) In the former case the gelling substances must be precipitated from solution. In the latter case the solution gels on cooling. The gel may be comminuted and dehydrated. These

products are stated to be commercially valuable as cosmetic and medicinal bases. (9)

Experimental

A. Leaves

I. Preliminary Experiments

The plant material for this phase of the investigation was supplied by Dr. Ivor Griffith. The recently dug plants (which had grown near Philadelphia) were received with the underground organs still attached to the leaves. They were identified as *Sansevieria zeylanica* by Dr. Theodor P. Haas, Department of Biology, Philadelphia College of Pharmacy and Science.

The moisture content of the leaves was determined by the toluene distillation method (10) on the day they were received. The leaves contained 91.8% of water.

The ash content of the leaves was determined on an air-dried sample (11). Before ignition, the moisture content of the sample was determined by the official Moisture Method for Drugs Containing no Constituents Volatile at 100° C.(12)

Moisture content:	8.80%
Total ash (moisture free basis):	14.96%
Acid-insoluble ash (moisture free basis):	0.10%

Preliminary experiments were performed on small quantities of juice obtained by passing leaves, previously cut into small pieces, through an electrically operated juice extractor. The liquid obtained in this way contained practically all of the leaf material except the fibers.

Some of the juice was shaken out successively with divided portions of petroleum ether, ether, and chloroform. The solvents were allowed to evaporate spontaneously. The petroleum ether residue was a very thin waxlike layer. The ether extract left a small amount of green residue and a thin waxy layer. The chloroform residue was negligible. In the process of shaking out the juice with ether, a small amount of a white solid material gathered in the interface. This material darkened after filtration from the ether solution and was not examined further.

The aqueous solution remaining was yellow in color, acid to litmus, and gave no reaction with Mayer's reagent or iodine-potassium iodide test solution. It gave a precipitate with tannic acid solution and became turbid when ferric chloride solution was added. It gave a white precipitate with lead acetate solution and a yellowish precipitate with lead subacetate solution. A precipitate formed when the liquid was boiled and also when alcohol was added. The solution gave a positive Molisch reaction for carbohydrates and a positive xanthoproteic reaction for proteins. A measured portion of the liquid was evaporated to dryness at 50° C. It contained 2.64% of solids.

A quantity of the green juice was heated with activated charcoal and filtered. The filtrate was pale yellow. On evaporation at 50° C. it yielded some white material and some yellow-brown residue. The residue was extracted with alcohol but little appeared to dissolve. The residue was then dissolved in water and treated with four volumes of alcohol. A curdy white precipitate formed and was filtered off.

The white solid partially darkened overnight. On heating, it charred but neither melted nor burned. In solution it gave no reaction with ferric chloride or iodine-potassium iodide. It did not reduce Fehling's solution and gave a doubtful Molisch test.

Portions of the charcoal used above in decolorizing the juice were extracted with the following solvents: alcohol, 2% sodium hydroxide, ethyl acetate, 1% hydrochloric acid, ether and petroleum ether. On evaporation of the volatile solvents, only minute amounts of amorphous or oily residues were obtained. The ethyl acetate residue was oily and yellow. The ether residue consisted of some yellow material and a colorless film. The sodium hydroxide extract was golden yellow. On acidification an amorphous precipitate formed, but the color of the solution was not affected.

In an attempt to find a more rapid and more efficient method of extracting *Sansevieria* juice two comminuted leaves were passed through a colloid mill. This was found impractical for large scale work because of friction and the intense heat developed, but the juice obtained was pale green, while the coloring matter adhered to the fibers, which were easily filtered off. The juice, about 75 cc., was shaken out with petroleum ether, ether, chloroform, toluene, and ethyl acetate in an unsuccessful attempt to remove the color. Boiling with charcoal also failed to decolorize the liquid, but it removed the opalescence.

The clear juice was examined by the lead method of Rochleder as described by Rosenthaler (13). The lead acetate precipitate yielded a fraction soluble, and another insoluble, in 8% acetic acid. Separation, however, was by no means complete. Each of these fractions yielded a few yellowish crystals. Those from the acetic-acid-soluble fraction appeared to be soluble in alcohol and insoluble in ether. They were sour to the taste, acid to litmus, and did not reduce Fehling's solution. Most of this material was lost through an accident during an attempt at recrystallization. The remainder, presumably impure, melted with decomposition at 160-161° uncorrected.

The crystals obtained from the acetic acid-insoluble portion of the lead acetate precipitate were sour to the taste and acid to litmus. They did not reduce Fehling's solution and they liquefied on heating. They could not be obtained in suitable condition for melting point determination.

The lead subacetate precipitate yielded a minute quantity of sticky yellow residue.

The filtrate remaining after the lead precipitations, when freed of lead and evaporated, left a quantity of sticky yellowish crystals which did not reduce Fehling's solution. On treatment with methanol, the yellow material dissolved, and the white crystals remained undissolved. These crystals, which were inorganic, were found to contain chloride ion. No cations were identified. Flame tests gave a transient potassium flame and a more lasting crimson flame. There was insufficient material for a more thorough qualitative analysis.

The methanol solution, on evaporation, left a sticky yellow residue possessing an unpleasant odor.

II. Systematic Examination of the Juice

In order to obtain sufficient juice for an investigation on a larger scale than hitherto, leaves were cut by hand into small pieces and passed through an electrically operated juice extractor. Since it took several days to prepare the quantity desired, each batch of juice was preserved with a few cc. of chloroform. The leaves used included some from the original batch, some which were growing in a flower pot (these gave a poor yield of highly mucilaginous juice), and some from a second batch of plants supplied by Dr. Griffith.

The yields of juice from individual leaves varied. A total of approximately 3200 grams of leaf was ground, and about 1870 cc. of juice were obtained. Results were by no means quantitative, but

as a rough approximation 1 cc. of the juice may be considered to represent 1.7 grams of fresh leaf.

The juice was green in color and thick with solid particles. On standing, the green cellular material tended to settle out, and the supernatant liquid was clear and yellowish. An attempt to filter the juice by suction was unsuccessful. It was filtered, therefore, through fluted filter papers. This was a very slow process. After being filtered twice and strained through cotton, the juice was still turbid and of a brownish-yellow color. This filtrate was used in the subsequent studies and will be referred to in this thesis as "juice".

1. Preliminary Tests

Forty cc. of the juice were used in the following tests: Reaction: acid to litmus and methyl red, but not to methyl orange.

Mayer's reagent: no reaction.

Iodine-Potassium iodide T. S.: no reaction when one drop was added, but a precipitate formed when an excess was added

Ferric chloride T. S.: red-brown precipitate

Fehling's solution: reduction

Alcohol: Sixty cc. of alcohol were added to about 15 cc. of juice. A white precipitate formed. It was filtered off after standing about two weeks. After drying overnight the precipitate still seemed moist and was of a waxy consistency. A portion of this precipitate was dissolved in 10 cc. of distilled water. The filtered solution was subjected to the following tests:

Alcohol: white precipitate

Reaction: neutral to litmus

Ferric chloride T. S.: flocculent reddish precipitate

Mayer's reagent: no reaction

Iodine-Potassium iodide T. S.: no reaction

Fehling's solution: no reaction

Tannic acid solution: no reaction

Molisch reagent: dark ring, forming red solution on shaking

Lead acetate solution: white precipitate

Xanthoproteic reaction: negative

Sodium fusion and qualitative analysis of the substance indicated the absence of sulfur, nitrogen, and halogens.

On ignition, the substance left a white ash soluble with effervescence in dilute hydrochloric acid.

After another day's exposure, the substance dried to a brittle brown mass. The color was apparently confined to the surface, for the powdered material was lighter in color. The substance was now at least partially water-insoluble.

2. Lead Precipitation of Juice

One thousand six hundred and fifty cc. (1650 cc.) of juice were heated to boiling. As the boiling point was approached, a white solid formed throughout the liquid. An excess (920 cc.) of 10% lead acetate solution was added. An hour later the mixture was filtered with suction. The yellowish-white precipitate was washed repeatedly with distilled water while on the filter. The precipitate (*A*) was allowed to dry in the air.

The clear filtrate combined with the washings was deep yellow in color. It was heated to 70° and treated with 1400 cc. of a lead subacetate solution containing 32.5 grams of lead subacetate. The yellow precipitate (*B*) was filtered with suction, washed, and allowed to dry in the air.

The filtrate was treated repeatedly with hydrogen sulfide until it was free of lead. The lead sulfide formed was filtered off and preserved. The filtrate (*C*) was treated with carbon dioxide for five minutes and allowed to evaporate spontaneously in a porcelain dish.

Precipitate *A*, weighing 47.4 grams, was extracted with alcohol in a Soxhlet extractor until the percolate was free of color. The alcoholic extract was green and gave no precipitate with potassium iodide solution, indicating the absence of lead. The coloring matter present in precipitate *A* had apparently been adsorbed rather than precipitated from the juice. The alcoholic extract (*AA*) was permitted to evaporate spontaneously.

Precipitate *A*, contained in an extraction thimble, was boiled for ten minutes in 200 cc. of 10% acetic acid. The acetic acid extract was bright yellow and contained lead. The lead was completely precipitated with hydrogen sulfide, and the lead sulfide formed was collected on a filter and preserved. The liquid was treated with carbon dioxide and filtered. The clear filtrate (*AB*) was allowed to evaporate spontaneously.

The main fraction of precipitate *A*, insoluble in both alcohol and acetic acid, was suspended in 300 cc. of water and freed of lead by hydrogen sulfide. The filtrate was treated with carbon dioxide, refiltered, and set aside to evaporate spontaneously (*AC*).

The lead sulfide obtained in this precipitation was boiled with two 100 cc. portions of distilled water. The combined aqueous extracts (*AD*) were freed of lead by hydrogen sulfide, treated with carbon dioxide, filtered and set aside for further investigation.

Precipitate *B* weighed 14.3 grams. A test performed on a small portion of it indicated it to be insoluble in hot alcohol. Accordingly, the entire precipitate *B* was powdered, suspended in 100 cc. of water, and treated with carbon dioxide for five minutes. The suspension was then treated with hydrogen sulfide until all the lead had been precipitated as lead sulfide, which was filtered off. The yellow filtrate (*B*) was treated with carbon dioxide, re-filtered, and allowed to evaporate spontaneously.

The lead sulfide thus obtained was boiled with two 100 cc. portions of distilled water. The combined aqueous extracts were freed of lead, filtered, treated with carbon dioxide, re-filtered, and permitted to evaporate spontaneously (*BA*).

All the lead sulfide which had not yet been extracted was combined and boiled with two 200 cc. portions of alcohol. The combined alcoholic filtrates were pale yellow and contained very little lead. On treatment with hydrogen sulfide, a brown colloidal solution was formed. After several days the lead sulfide had coagulated. The mixture was filtered. Upon spontaneous evaporation of the filtrate a minute amount of yellow residue was obtained. This was not examined further.

3. Examination of Residues

AA. On evaporation to dryness, this solution yielded a minute amount of green residue possessing some odor.

AC. This solution evaporated, leaving a moist yellowish crystalline residue. This was transferred to a filter paper and allowed to dry in a desiccator. When dry, the extract weighed 6.0 grams.

Residue *AC* was triturated with several portions of ether. The yellow insoluble portion of the residue appeared moist and gummy. The ether solution was filtered and allowed to evaporate.

Ether-insoluble fraction

This was dissolved in a few cc. of distilled water and precipitated by the addition of five volumes of alcohol. The flocculent precipitate was collected on a filter and washed with alcohol. On the filter paper the material formed a translucent, jelly-like mass, but on drying in

the air it shriveled into a small quantity of hard, opaque fragments. It was not examined further.

Ether-soluble fraction: Identification of Aconitic Acid

On evaporation of the ether, about three grams of a white crystalline powder were obtained.

These crystals melted with decomposition at varying temperatures, depending on the rate of heating. Typical melting ranges were 183.5-184.5°, 185-187°, and other figures as high as 191°.*

Elementary analysis revealed the absence of sulfur, nitrogen, and halogens.

An 0.2 gram sample of the crystals was soluble in 3 cc. of water as well as in an equal volume of ether. The aqueous solution was acid to litmus.

An aqueous solution of the crystals decolorized potassium permanganate solution instantly. It gave no reaction with ceric nitrate reagent, indicating the absence of hydroxyl groups.

The neutral equivalent of the compound was determined on two samples by the method given by Shriner and Fuson (14).

	1.	2.
Weight of sample	0.1108 Gm.	0.1558 Gm.
Volume of NaOH (N=O.1206)	15.01 cc.	21.12 cc.
Neutral Equivalent	61.19	61.16

The evidence thus far obtained suggested the possibility that the unknown might be aconitic acid (propene-1,2,3 tricarboxylic acid) since the latter is a water-soluble acid (neutral equivalent 58) easily oxidized by potassium permanganate and possessing no hydroxyl groups. Furthermore, the variable decomposition temperature of aconitic acid has been noted by Bruce (15).

The following color reaction (16) was applied to small samples of the unknown acid and of aconitic acid from a commercial source. In each case the results were the same:

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* All temperatures reported in this thesis are uncorrected. All melting point determinations were made with the same thermometer. This thermometer was checked against U. S. P. Melting Point Reference Standards, with the following results:

	m.p. listed	m.p. observed
Vanillin	81-83°	81.5-83°
Acetanilid	114-116°	114-116°
Sulfapyridine	190-193°	189-191.5°

A few small crystals were mixed with a few drops of acetic anhydride. On addition of one drop of pyridine, an immediate color change occurred. The solution first became yellow, changing rapidly to red and finally to violet-red.

Preparation of a Derivative

The following procedure was carried out both with a sample of the unknown and an authentic sample of aconitic acid:

One-half gram (0.0029 mole) of acid was dissolved in 3 cc. of distilled water and was neutralized to phenolphthalein with 10% sodium hydroxide solution. The solution was then made slightly acid to litmus with 10% hydrochloric acid. Next 2.5 grams (0.009 mole) of *p*-bromophenacyl bromide were added, followed by 10 cc. of alcohol. The mixture was refluxed on the water bath.

The *p*-bromophenacyl bromide tended to dissolve as the temperature rose, but after five minutes crystals began to form in the solution. After fifteen minutes the liquid was choked with crystals, and heating was therefore discontinued. The mixture was cooled and the crystals were filtered with suction and washed. The light yellow product was placed in a flask and boiled with 5 cc. of acetone and 20 cc. of alcohol. The crystals did not dissolve to any great extent, but their color was removed. The now white crystals were filtered with suction and dried.

melting point of authentic tri-p-bromophenacyl aconitate	188-189.5°
melting point of tri-p-bromophenacyl derivative of the unknown	187.5-189°
mixed melting point	187.5-189°

The melting point reported for this derivative is 186° (17).

The crystalline compound isolated from residue *AC* was thus identified as aconitic acid.

A survey of Wehmer (18), who covers the literature up to 1934, and of the indices of all subsequent volumes of Chemical Abstracts, reveals that aconitic acid has not previously been reported in any species of the *Liliaceae*.

A Note on the Phenacyl Ester of Aconitic Acid

In connection with the characterization of aconitic acid described above, the phenacyl ester of an authentic sample of aconitic acid was prepared in order to study the feasability of this derivative before risking any of the unknown.

The ester was prepared as follows: 0.5 gram (0.0029 mole) of aconitic acid (Pfizer; melting point 189-191° dec.) was dissolved in 3 cc. of distilled water and made just alkaline to phenolphthalein with 10% sodium hydroxide solution. The solution was made just acid to litmus with 10% hydrochloric acid. Two grams (0.0100 mole) of phenacyl bromide and 10 cc. of alcohol were added next. The mixture was refluxed on the water bath for three hours. The supernatant liquid was decanted from a yellow-red oil which had settled to the bottom of the flask. The oil was covered with alcohol and kept in a refrigerator overnight. On warning to room temperature, crystallization occurred. The crystal masses were filtered with suction and recrystallized from alcohol containing a little acetone, using activated charcoal. Just below the boiling point, the yellow solution deposited white crystals. When filtered, washed, and dried, these melted at 101.5-103°. The melting point was unchanged by another recrystallization from alcohol.

Rather and Reid (19) prepared the phenacyl esters of a large number of organic acids. For triphenacyl aconitate they list a melting point of 90°. These authors call attention to the fact that the ester they obtained was yellow in color, whereas the phenacyl esters of the other acids were white. In view of the difference in color and melting point between the ester obtained in this investigation and that obtained by Rather and Reid, further work was undertaken to characterize the ester prepared in this study.

An attempt to determine the saponification equivalent of the ester failed because immediately on the addition of alcoholic potassium hydroxide to the sample, a red solution resulted. This not only interfered with the subsequent titration but probably indicated some chemical reaction other than hydrolysis.

A second and a third batch of the ester were prepared, using double quantities of reagents. It was noted in each preparation that after fifteen minutes of refluxing, the reaction mixture suddenly became cloudy and of a brownish color. After another hour the mixture cleared, a red oil settled to the bottom, and the supernatant liquid became yellow. Low yields of the ester were obtained because of the difficulty of separating it from a red oil which tended to color the crude product yellow.

The third batch of the ester was made using once-recrystallized phenacyl bromide which had been synthesized on the previous day.

After four recrystallizations of the product from alcohol, a constant melting point of 102-103° was obtained. A sample of this product, after being dried in a vacuum desiccator over calcium chloride during a week-end, was submitted to Dr. Carl Tiedcke, 366 Fifth Avenue, New York, for micro-determination of the carbon and hydrogen content.

Calculated for $C_{30}H_{24}O_9$	(molecular weight 528.49):	
	carbon 68.18%	hydrogen 4.57%
Found	carbon 67.52%, 67.35%	hydrogen 4.49%, 4.62%

Based on the foregoing observations, it appears that the compound described by Rather and Reid (19) was impure, and that the tri-phenacyl ester of aconitic acid is actually a white crystalline solid, m.p. 102-103°.

AB. A minute amount of crystalline residue, mixed with some brown syrupy material, was obtained. The crystals were soluble in ether and were thus separated from the amorphous substance. On evaporation of the ether, a few white crystals were formed. These were sour to the taste, decomposed at about 184°, and gave the color reaction previously described for aconitic acid, when treated with acetic anhydride and pyridine.

AD. On evaporation of the solution over the water-bath, 2.2 grams of brownish crystals were obtained. Some of this material was water-soluble and alcohol-insoluble. This material was primarily inorganic.

A small fraction of residue *AD.* was alcohol-soluble but ether-insoluble. In alcoholic solution this formed a white precipitate when ether was added. The precipitate was separated by decantation of the mother liquor and washed with a little ether. In contact with the air, the white solid darkened rapidly and liquefied. This material was not examined further.

B. Upon spontaneous evaporation solution *B* assumed the appearance of a dark brown viscid liquid. This was taken up in absolute alcohol and filtered clear. Addition of ether to the alcoholic solution produced a gummy, dark precipitate, an aqueous solution of which reduced Fehling's solution.

The ether-alcoholic solution was allowed to evaporate spontaneously. The syrupy residue was dissolved in distilled water. The solution strongly reduced Fehling's solution and gave a negative

iodic acid test. Under the conditions of this test, fructose, sorbose, sucrose, d-arabinose, l-xylose, and rhamnose are oxidized; while glucose, mannose, and galactose are not (20).

An attempt was made to prepare an osazone, using the aqueous solution. Some dark-colored crystals formed on cooling the reaction mixture. An attempt to recrystallize these failed.

BA. This residue was brown, syrupy, and small in amount. An aqueous solution of it was used in an attempt to prepare an osazone. When the reaction mixture was cooled, a precipitate seemed to form, but the dark color of the original solution masked the result.

C. This residue represented those constituents of the original juice not precipitated by either lead acetate or lead subacetate. It was dark brown in color, contained many rosettes of crystals, and possessed an unpleasant odor.

A small portion of residue *C* was dissolved in a little distilled water and the following tests were performed:

Reaction: neutral to litmus
Fehling's solution: reduced
Molisch reaction: positive
Mayer's reagent: negative
Iodine-potassium iodide T.S.; negative.
Ferric chloride T.S.: red solution. This was probably due to the presence of acetate ion, as solution *C* originally contained some free acetic acid.

Treatment of residue *C* with cold methanol produced a brown solution and an insoluble white crystalline residue. Fusion tests of the crystals indicated that they were mainly inorganic in nature. They did not reduce Fehling's solution. The methanol-soluble fraction possessed reducing properties.

III. Studies on the Dried Leaves

In order to obtain an over-all picture of the chemical constituents of the entire leaf of *S. zeylanica,* it was decided to investigate the whole leaves in the dried condition. Accordingly, fifty pounds of plant material grown in Florida were obtained through the S. S. Pennock Co. of Philadelphia. These plants were young and contained much less rhizome and root material than the plants previously studied.

Moisture was determined by the toluene distillation method on a sample from one leaf. The sample contained 86.6% of water.

It was noted that the leaves could not be dried at room temperature. The waxy coating of the leaves presented rapid loss of water, and prolonged exposure of the whole leaf to the air resulted in wilting rather than drying.

A small quantity of leaf was comminuted by hand and placed in a drying oven at a temperature of 30-35°. The dry material was boiled with water and filtered. The following tests were applied to the filtrate:

1. Litmus: acid reaction
2. Fehling's solution: reduction
3. Molisch reagent: positive
4. Ferric chloride T.S.: precipitate
5. Iodine-potassium iodide T.S.; turbidity
6. Mayer's reagent: slight turbidity
7. Alcohol: flocculent precipitate
8. Preparation of osazone: Four cc. of the filtrate were used.

Yellow crystals of osazone were formed after several minutes. Microscopically these crystals resembled long needles.

A 5 cc. sample of the filtered juice was used in the preparation of an osazone. Crystals were noticed almost immediately. They melted at 199-203°. Cellobiose osazone melts at 198°, lactosazone at 200°, D-galactosazone at 201°, glucosazone (fructosazone) and D-mannosazone at 205°, and maltosazone at 206° (21).

The entire batch of Florida-grown leaves was comminuted by hand into smaller pieces which were passed through a Wiley mill. Thus chopped to a greater extent, the material was dried in an oven maintained at 30-35° (temperature at top). Heating was intermittent, the oven being turned off over nights and over week-ends. The chopping and drying process was spread over a month's time. It was noted that material which was completely dry and brittle when the heat was removed at night, re-absorbed moisture and was quite plastic in the morning.

The dry leaf material was ground in a mill to a rather coarse green powder. This powdered Sansevieria leaf was stored in large glass jars, and was used in the experiments which follow.

1. Selective Solvent Extraction

Forty (40.0) grams of drug were packed in a Soxhlet extraction apparatus and extracted with the following solvents: petroleum ether, ether, chloroform, and alcohol. (For extraction with distilled water the Soxhlet apparatus was not used.) Since the oven-dried leaf was found by the toluene distillation method to contain 6.00% of water, the percentages of extractive in Table I are based on 37.6 grams of dry leaf.

TABLE I

Solvent	Weight of Extract (Gms.)	%
1. Petroleum ether	0.595	1.58
2. Ether	0.76	2.02
3. Chloroform	0.63	1.68
4. Alcohol (95%)	6.85	18.22
5. Distilled water	6.05	16.09

Extraction with distilled water was performed as follows: The air-dried marc from the first four extractions was treated with 300 cc. of boiling water and heated on the water bath with occasional stirring for 1½ hours. The liquid was then expressed from the drug, since the latter held the water tenaciously. The water used was not recovered entirely, and therefore the weight and percentage of distilled water extract listed in Table I are low. The aqueous extract was made up to a definite volume and an aliquot portion was evaporated on the steam bath. The residue was dried in a desiccator and weighed.

Petroleum ether extract. The residue was stirred with a few cc. of 2% hydrochloric acid. The acid solution gave no reaction with Mayer's reagent, Iodine-potassium iodide T.S., and Molisch reagent.

The residue contained a white or light yellow, waxy material, not readily soluble in alcohol, ethyl acetate, benzene, or even petroleum ether. The quantity obtained was insufficient to permit further study.

Ether extract. The residue was black and sticky. It contained some white material which had precipitated from the ether solution during the extraction.

A dilute sulfuric acid extract of the residue gave a positive Molisch reaction. An aqueous extract of the residue reduced Fehling's solution and yielded a small amount of an osazone. The presence of traces of reducing sugar may be explained by the fact that the ether used was not anhydrous.

The residue could be precipitated from alcoholic solution by water.

Chloroform extract. The residue contained some material which had precipitated from the chloroform solution during extraction. Most of the residue was dark green, while a little of it was practically free of color. The dark residue was brittle. It was at least partially soluble in benzene and in aqueous potassium hydroxide.

A dilute hydrochloric acid extract of the chloroform residue gave no reaction with Mayer's reagent, Iodine-potassium iodide T.S., Ferric chloride T.S., Fehling's solution, or Molisch reagent.

Alcohol extract. The alcohol extract contained inorganic crystals which had settled out of solution during extraction.

The alcoholic solution was acid to litmus. On addition of water, an insoluble layer of liquid settled to the bottom of the container. This layer was found to have the odor of chloroform. Later the odor of chloroform was noted in the marc in the Soxhlet extractor. Incomplete evaporation of the chloroform after extraction No. 3 accounted for the presence of chloroform in the alcohol extract.

The bulk of the green alcoholic solution was treated with a large excess of water to precipitate the chloroform, which removed the green pigments from the hydro-alcoholic layer. The latter solution was concentrated on the water bath and the yellow concentrate was used in the preparation of an osazone. An osazone formed, but its reddish-brown color indicated that it was quite impure.

Distilled water extract. The residue was amorphous and brown in color.

Small portions of the aqueous solution yielded a white precipitate with alcohol and with lead acetate solution respectively.

On standing, the bulk of the aqueous solution developed a growth of an unidentified species of *Penicillium*. As the chemical composition of the extract was thus altered, no further experiments were performed.

2. Attempted Preparation of the Gelling Constitutents (9).

One hundred and fifty grams of powdered leaf were macerated overnight in 750 cc. of chloroform water. The liquid was expressed and the marc was placed in a large beaker and covered with distilled water. A solution containing 9.4 grams of Calgon (sodium hexametaphosphate) was added and the mixture was boiled for a few minutes. The hot liquid was drained through a pledget of cotton. The green opalescent liquid was divided into three portions:

1. A few cc. were chilled in the refrigerator overnight, but a gel was not formed.

2. Half of the liquid was treated with two volumes of acetone. A precipitate formed, and was filtered off after standing a few days. The other half of the liquid was treated with two volumes of alcohol, and the resulting precipitate was filtered. In both cases the solid material, on drying in the air, shriveled markedly in volume and became brittle. The product was not water-soluble, as claimed in the patent referred to (9), but these results are not considered completely significant because the procedure followed was a modification of that described in the patent.

B. Rhizomes and Roots

I. Selective Solvent Extraction

Forty-five (45.0) grams of the air-dried and coarsely powdered underground portions of the plants supplied by Dr. Griffith were placed in a Soxhlet extraction apparatus and exhausted with the following solvents: petroleum ether, ether, chloroform, and alcohol. For extraction with distilled water the Soxhlet apparatus was not used. The weights and percentages of the various extractives are listed in Table II.

Table II

Solvent	Weight of Extract (Gms.)	%
1. Petroleum ether	0.25	0.55
2. Ether	0.39	0.87
3. Chloroform	0.75	1.67
4. Alcohol	8.50	18.89
5. Distilled water	6.40	14.22

Petroleum ether extract. The solution was lemon-yellow in color. A 1% sulfuric acid extract of the petroleum ether solution gave no reaction with Mayer's reagent, Iodine-potassium iodide T.S., Ferric chloride T.S., and Molisch reagent.

Two per cent sodium hydroxide did not extract anything from the petroleum ether solution.

The residue obtained on evaporation of the petroleum ether was orange-yellow in color, waxy, and had an odor characteristic of the underground portion of the plant. The residue was partially soluble in cold alcohol, forming a yellow solution which became cloudy on the addition of water.

Ether extract. The ether extract had a lemon-yellow color and contained undissolved material.

The residue obtained on evaporation of the ether was primarily yellow, amorphous, sticky, and had the same odor as the petroleum ether extract.

The residue was treated with 100 cc. of ether. Some white material did not dissolve readily. This was separated by decantation of the ether solution into a separatory funnel. The white material was found to be soluble in hot alcohol, insoluble in hot water, but soluble in hot sodium hydroxide solution. It had no sharp melting point but melted gradually around 80°.

The ether solution in the separatory funnel was shaken out with 1% hydrochloric acid. The acid solution gave a precipitate with both Mayer's reagent and Iodine-potassium iodide T.S. The precipitate obtained with the latter reagent dissolved on standing in an excess of reagent. In fact, the acid solution, after standing a few hours, no longer gave a positive alkaloidal reaction.

The ether solution was next washed with water and shaken with 2% sodium hydroxide solution. The pale yellow color of the ether solution changed to a deep orange-red color which was extracted by the alkali. The alkaline extract was acidified and the precipitate which formed was extracted with ether. On evaporation of the ether, a red, resinous residue was obtained, which had a characteristic, pleasant odor.

The original ether solution was allowed to evaporate. The residue was greenish yellow, of a fatty or resinous consistency, and possessed a characteristic odor.

Alcoholic solutions of the various fractions of the ether residue gave no color reaction with Ferric chloride T.S.

Chloroform Extract. The chloroform solution was washed with water and shaken with 2% sodium hydroxide solution. No precipitate was formed when the alkaline solution was acidified.

Evaporation of the chloroform solution yielded a yellow, powdery residue having the characteristic odor of the rhizomes and roots. The residue was insoluble in petroleum ether. It dissolved in hot alcohol, a flocculent white precipitate being formed on addition of water to the alcoholic solution. The residue also dissolved in hot sodium hydroxide solution, a white precipitate being formed on acidification.

Alcohol extract. The alcohol solution was of a deep orange color and contained a small amount of white material. The solution was acid to litmus and methyl red, it gave no color reaction when treated with Ferric chloride T.S., and strongly reduced Fehling's solution.

The bulk of the alcoholic solution was evaporated nearly to dryness on the water bath. The resulting syrup was taken up in water and treated with an excess of lead acetate solution. The precipitate was removed by filtration and the filtrate was freed of lead by the addition of a solution of trisodium phosphate. The precipitated lead phosphate was filtered off. Part of the pale yellow filtrate was used in the preparation of an osazone. The remainder was evaporated nearly to dryness and placed in the desiccator. Portions of the syrupy residue (A) were used in the tests described below.

melting point of unknown osazone	203-204°
melting point of glucosazone made from authentic sample of glucose	201-203°
mixed melting point	202-203.5°

The residue (A) was oxidized by iodic acid (20) to about the same extent as an authentic sample of fructose which was tested simultaneously.

The only reducing sugar yielding the same osazone as glucose and oxidized by iodic acid is fructose (20).

In order to confirm the presence of fructose in residue (A), the resorcinol test was applied both to the unknown and to 1% aqueous solutions of authentic sample of pure fructose and glucose. To make

the solution of the unknown, as much of residue (A) as could be lifted by the tip of a stirring rod was dissolved in 3 cc. of distilled water.

Appropriate amounts of the solutions of the sugars were mixed with Selivanoff's reagent (22) and heated in boiling water for two minutes. The test tubes were immediately removed from the water bath and the color of each solution was noted. The results of the test are summarized in Table III.

TABLE III

Tube	Sugar	Amount of Sugar	Vol. of Reagent	Observations
1	Blank		2 cc.	Colorless
2	Dextrose	1 mg.	2 cc.	Faint tinge
3	Dextrose	5 mg.	2 cc.	Faint tinge, slightly darker than 2
4	Fructose	1 mg.	2 cc.	Cherry-red
5	Fructose	5 mg.	2 cc.	Cherry-red darker than 4
6	Unknown	1 drop	2 cc.	Light red, much darker than 3
7	Unknown	0.5 cc.	2 cc.	Cherry-red, darker than 5
8	Unknown	0.5 cc.	Reagent without resorcinol	Colorless

The resorcinol test is positive for fructose and those polysaccharides which yield fructose on hydrolysis (23). Thus the above experiments have shown that fructose is a constituent of the underground portions of *S. zeylanica.*

Distilled water extract. The air-dried marc from the first four extractions was treated with boiling water and digested on the water bath for one hour. The liquid was then expressed, strained through cotton, and made up to 500 cc. in a volumetric flask. Fifty cc. of the straw-colored, opalescent solution were pipetted into a tared beaker and evaporated on the water bath. The residue was dried in the desiccator and weighed.

Because of the affinity of the marc for water and the incomplete recovery of the water used for extraction, the weight and percentage of water-soluble extract given in Table II should not be considered more than approximate.

The distilled water solution was neutral to litmus and methyl red. It gave no reaction with Mayer's reagent, Iodine-potassium iodide T.S., Ferric chloride T.S., and Fehling's solution. It gave a positive Molisch reaction and a small amount of precipitate with alcohol.

Summary

1. A phytochemical study has been made of the fresh leaf juice, the dried leaves, and the dried rhizome and roots of *Sansevieria zylanica* (Willd. Fam. *Liliaceae*).

2. Aconitic acid was isolated from the juice.

3. Triphenacyl aconitate was prepared from an authentic sample of aconitic acid and analyzed. This ester is a white crystalline solid, melting point 102-103°. It would appear that the melting point of 90° which has been reported in the literature (19) pertains to an impure sample.

4. The juice was found to contain reducing sugars, inorganic salts, and a white, amorphous, unstable substance soluble in water but insoluble in alcohol.

5. In the dried rhizomes and roots, indications were found of the presence of an alkaloid, an acid resin, a neutral resin, and material of a waxy nature. These have previously been reported (2). Salicylic acid has also been reported, but no indications of its presence were found in this investigation.

6. The presence of fructose in the rhizomes and roots was demonstrated, although the sugar was not isolated in a pure condition.

Acknowledgments

The authors gratefully record and acknowledge the guidance of Dr. Ivor Griffith in recommending and furthering the foregoing project. The help of the following is gratefully acknowledged: Dr. Arthur Osol, Dr. Marin Dunn, Dr. Nathan Rubin, Dr. Theodor Haas and Mr. Elof Johnson.

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F. GOWLAND HOPKINS, GLUTATHIONE, AND I

By T. Swann Harding

THE recent death of Sir F. Gowland Hopkins forcibly reminds me of my brush with this celebrity some twenty years ago. At the time I was engaged on research in the nutrition of dairy cattle, working under the late Edward B. Meigs and with C. A. Cary who is now in charge of Bureau of Dairy Industry investigations on the nutrition and physiology of such animals. During these researches I stumbled quite by accident upon a substance in cow's blood which appeared to be Hopkins' glutathione. After I personally had worked up over five hundred gallons of fresh pig's blood to secure an ounce or so of the substance, our examination of it and of our procedures in its preparation, made it impossible for us to confirm Hopkins' previously published results.

It will be remembered that Hopkins announced the isolation of glutathione by himself in 1921 (*Biochemical Journal 15,* 286); a later paper by Hopkins and Dixon gave more detail the following year (*Journal of Biological Chemistry 54,* 529). Still later the constitution of glutathione as diglutaminyl-cysteine was presumed conclusively established by Quastel, Stewart, and Tunnicliffe in 1923 (*Biochemical Journal 17,* 586) and the substance was reported to have been synthesized in 1925 by the latter two investigators (*Biochemical Journal 19,* 194). Hopkins believed glutathione to be absent from mammalian blood, judging by the nitroprusside test. We, however, began in 1925 to feel certain that the material was present in cow's blood and that it was not a dipeptide as reported by Hopkins and associates.

However Hopkins was Hopkins, a distinguished research worker of international renown, and we were just unknown little shots, especially the present writer. It was therefore deemed necessary for us to reexamine our own work and, if possible, to secure results which confirmed rather than contravened Hopkins'. To write to so great a man, taking the matter up with him directly, was simply out of the question. So, since this could not be done officially, I impertinently sat down and did it personally from my residence.

As I kept no copies of my letters, a lifelong habit, I am a little vague about the precise significance of Hopkins' replies, but I am

absolutely certain that they have more historical importance than my letters. Since then I have left laboratory work for scientific editing and writing—the laboratory was much better off—and have grown rusty in what was then my specialty. But the other day, after reading the long accounts of Hopkins' distinguished career in various British scientific and medical journals, I decided to try to find "the letter" he wrote to me.

Oddly enough I was able to locate the correspondence, a distinct novelty with my files, and there were four letters. In view of the fact that Hopkins was still at the beginning of his work on glutathione, and of the further fact that he usually wrote painfully in longhand, and felt obligated to expend so much space explaining to me the difficulties under which he labored, I think they deserve the light of day. The first of them was typewritten, was dated January 20, 1926, and was headed University of Cambridge, School of Biochemistry, Sir William Dunn Institute, Tennis Court Road, Cambridge, and it ran thus:

Dear Dr. Swann Harding,

(I was not "Dr." and am not now but have often thought of claiming the degree since Hopkins so graciously conferred it upon me. tsh.)

I was truly sorry to read that your Christmas and New Year's feelings were so disturbed by Holden's paper. His discovery of glutathione in the red corpuscle was an accident; he was looking for something else. As a matter of fact, since his publication he has been continuing work on the subject, and has some fresh results. Nevertheless, I hope very sincerely that you will ignore this and publish your own work. I have read your "Canonical Propositions" and from these it is quite sure that you have found that blood contains glutathione. In my original paper I was, I think, somewhat careless in speaking of its absence from blood, as I was thinking always of plasma. But the fact that a misstatement was made fully justifies you in publishing evidence obtained before Holden's paper appeared.

The trouble is that my method of isolating glutathione is useless when the quantities are small, because of the loss at each stage of the elaborate process. For instance, we can get 20 gms. from 50 kilos of yeast, while from 5 kilos of yeast one

may get no final product at all. If only you could improve the process, I should be greatly rejoiced. I am very much interested in your Proposition 14. (I wonder what it could have been. I must have sent him an astoundingly formal document. tsh.) This suggests a line of research quite independent of Holden's. I trust you will go on with it.

It is nice to read of Dr. Meigs' kind opinion of myself. I certainly heartily reciprocate. I always think of him as one of the nicest and kindest men I ever met. Pray give him my kind regards.

Sympathising with your slight loss of priority in research (I have often suffered similarly myself).

Believe me, Yours sincerely, F. G. Hopkins.

P. S. I am sending you a copy of my last paper on glutathione, but unhappily all my earlier ones are exhausted.

Nor was that his "last" paper by any means. What had happened? Holden, a colleague of Hopkins, had claimed to have isolated glutathione from sheep blood corpuscles (*Biochemical Journal 19, 727,* 1925) right while I had been restrained from publication or from communicating with Hopkins earlier. Indeed editors of appropriate scientific journals in this country displayed no enthusiasm whatever to accept a paper by a young upstart who persisted in confuting the respected authority in the field. As a matter of fact we were beaten to the punch even in Canada.

For there, at the University of Toronto, unknown to us as well as to Hopkins, George Hunter and Blythe Alfred Eagles were hard at work on the nonprotein sulfur compounds of blood, which included a critical study of glutathione. They prepared the substance from yeast, blood, and liver, analyzed it, concluded that it could not possibly be diglutaminylcystine, and suggested that it was not a simple dipeptide of cysteine and glutamic acid (*Journal of Biological Chemistry, lxxii,* 147, 1927) in work done during 1926. Later Eagles joined Cary and me in our laboratory; for a while Eagles and I also worked on glutathione with the late Treat B. Johnson at Yale.

Meanwhile Cary and I had managed to appear before the Society for Experimental Biology and Medicine, and had published a brief note on Glutathione in Blood and its Utilization in Milk Secretion (*Proceedings 23,* 319, 1926). But we had aired our suspicions

of Hopkins' formula for glutathione only incidentally. Nevertheless I maintained an active correspondence with Hopkins, pounding at him to have his work reviewed, but apparently the publication of Hunter and Eagles influenced him much more than my personal communications.

His next letter to me, like the other two later, was written in longhand and dated 28.4.26 from Saxmeadham, 71, Grange Road, Cambridge. In this instance I had apparently written to him, waited for a long time for a reply, and finally either written again or sent a copy of the laboratory notes from which I wrote earlier. He replied:

> Dear Mr. Harding: I am extremely sorry that your letter written in February last received no answer. I was, till your last communication arrived, fully under the impression that you had heard from me. I have indeed had some trouble in finding out why you had not! It has gradually transpired that after dictating an answer I handed it over to Holden for perusal and comment—a circumstance which I forgot. Holden it seems returned it to my Secretary who omitted to remind me that my reply had never been dispatched. After the receipt of your last it was found in our office.
>
> I am truly sorry for this lapse from courtesy, and can only plead for forgiveness as an overbusy man. I have nearly fifty research workers in my laboratory now, and as, in addition to a great deal of teaching, I have (such are Cambridge institutions) to run my department as a self-contained business, with little or no help from the University, there is also no little administrative worry to face. You will understand that, if any lapse in the systematic treatment of correspondence occurs, it is easy under the circumstances to forget it. My burden is at the moment too much for one pair of shoulders!
>
> I thank you for sending me the reprint of your paper. (Mine and Cary's, tsh.) The behavior of glutathione in the mammary gland interests me—needless to say, very much. It is significant that when an organ is active it should make demands upon the blood for this constituent. (We thought we had evidence that the cow's mammary gland removed glutathione from the blood perfusing it as it was active in milk secretion, tsh.) Like yourself I find it a bit difficult to understand how the glutathione

gets so readily out of the corpuscles for they seem to be more or less impermeable to it. To be frank I am myself still very vague with regard to the functions of the substance anyhow. I have not yet found a cell oxidation of obvious physiological importance, which it can be clearly shown to influence.

I do not think that Holden, even now, has ever done a full analysis of the product from blood, though its general behavior agreed with products prepared from tissues. I do not wonder that you found its isolation difficult.* I imagine that the process of isolation *might* need some modification in the case of red corpuscles. That Holden actually isolated the product by means of phosphotungstic acid, while I have used that reagent at one stage for removing admixtures, is explained by the circumstances that, while oxidized gt. is fairly completely pptd. by phphstgic., the reduced form is scarcely pptd. at all and is soluble in excess. Holden oxidized before precipitating; I have always used the reagent when glut. is reduced. In the latter case the chief thing it removes is hypoxanthin, of which the red corps. must contain almost nil. Holden used, not citrated, but oxalated blood.

The paragraph which Dr. Meigs deleted from your ms. contains it seems to me something very interesting.

Most sincerely yours,

F. G. Hopkins

(* I always find it difficult to get proportionate yields when small quanties of yeast or muscle are used. From a pound or two of either the final product may be nil. So much loss inevitably occurs during the many precipitations.)

We, however, were becoming more certain all the time that glutathione did occur in mammalian blood, which was why I worked up the five hundred gallons of pig blood I secured by holding buckets under the heads of the animals on the killing floor as they were stuck, and citrating immediately. We also felt that the substance could not be a dipeptide, yet the synthesis published from Hopkins' laboratory seemed conclusive. His next letter to me, from the same address, was dated 12 xii. 27, and ran thus:

Dear Mr. Swann Harding:

Much as I have disliked keeping your letter (or, rather, your Report and Questions) so long without acknowledgment, I really

could not help it. I was so pressed with other work during the month of November, that I could give no thought to the Glutathione question. I have written to Dr. Meigs at some length explaining my position and have asked him to show you my letter. (He may have done so; by now Dr. Meigs felt confidence enough in Cary and me to write Hopkins, tsh.) The fresh attack upon the isolation problem necessitated by the publications of Hunter and Eagles has been for me a matter of extreme difficulty. I get no leisure whatever for personal research during the University Terms, and, unhappily, nearly the whole of the summer vacation this year was compulsorily spent away from my laboratory. My fresh attack on the matter has therefore progressed terribly slowly.

In a desire to get a better yield we have, since learning of Hunter and Eagles' experience, modified the latter stages of the method, as you will find on reading my letter to Dr. Meigs. To say the truth I have, therefore, so far, not returned to the original process at all, though I mean during the present vacation to try and carry through the separation by its means from two distinct samples of yeast.

The first result of the modified method was that we found ourselves to be dealing with glutamyl-cysteine mixed with another dipeptide, and when in this association they have proved very difficult to separate. As I have told Dr. Meigs, to detail fully our experiences, such as they are, would take a long time, and only during the Xmas week shall I have leisure to survey properly the scattered notes gathered through a period of some fifteen months of interrupted work. As soon as possible after Xmas I mean however to write some sort of paper (probably not a final one) for the J. B. C. The typescript of this shall be sent you when it is written. (It never was, tsh.)

I fear my answers to your questions are now too late to be of use. In any case as I have not repeated the original procedure for nearly two years and have only worked with yeast of late I am not sure I could be helpful with your attack on the separation from blood.

1) You ask about the lead acetate used. I have always employed a saturated solution of "normal" lead acetate—Pb A_2. 3 H_2O. Years ago in my original endeavor to tease out a

nitroprusside-test-yielding substance I employed the neutral salt because I found it *more selective* as a precipitant than the basic salt. It throws down the –SH form from dilute solutions, but the S-S form only from concentrated solutions and then very imperfectly. It is indeed an imperfect precipitant even for the former. Apart from ppt. variations the precipitate is moreover soluble in excess of the reagent, and with pptn. much on the acid side it is soluble apart from the excess. This is one reason why I have modified the original form. With regard to precipitation by lead if, as you find, the glutathione from blood is largely in the oxidized form (which is certainly not the case with fresh yeast) I can understand that you may need to use the basic salt, though I still think it is less selective.

2) With regard to phosphotungstic acid I use either a 10% aqueous solution or a 10% solution in 5 percent H_2SO_4. One seems to get the same result with either. The fact that Holden used the acid as a precipitant and I the same as a "defecant" is explained once more by the difference in the –SH and the S-S compounds. The former is not ppd. (save in very concentrated solutions); the latter is precipitated with fair completeness by phosphotungstic acid.

If the last volume of Oppenheimer's "Die Formente" ("Methods") has reached you, you will find I have described a method defecating with uranium acetate and starting with a precipitation by mercury. Unfortunately when this was written we had not realized that the product so obtained contained, some at least, of our second dipeptide.

You will have the typescript of the paper as soon as possbile. (It was never gotten to me, tsh.)

With kind regards,

Sincerely,

F. Gowland Hopkins.

The very next event was publication of Hopkins' famous retraction in the *Journal of Biological Chemistry 84*, 269 (1929) entitled "On Glutathione: A Reinvestigation." It was one of the most remarkable articles that ever appeared from a truly great investigator, for it essentially admitted that the previous analyses and syntheses of glutathione were incorrect (how the synthesis could have been I

shall never know) but, while it quoted Hunter and Eagles' work as throwing doubt upon the constitution of glutathione, it mentioned me and my anguished personal communications not at all. Yet these had come to Hopkins's attention much before he knew of the Hunter-Eagles' work.

In this astounding paper Hopkins confessed he had been reluctant to reopen his investigation, especially after a paper by Johnson and Voetglin seemed to offer evidence in favor of the original formula. He went on: "The grave discomfort involved in making an admission of previous error is mitigated by the circumstance that I am now able to describe a method, not without special interest in itself, which with ease and rapidity separates from yeast and from red blood corpuscles a pure crystalline thiol compound with a peptide or quasi-peptide structure." This compound he then recognized as a tripeptide, containing glycine, in addition to cysteine and glutamic acid. To quote further:

"It is sure . . . that the original preparation of glutathione as described in 1921 must certainly have contained glycine, and indeed almost certainly contained, as did the intermediate preparations just discussed, a large proportion of the tripeptide. I now find it hard to understand how I originally missed the presence of glycine, so easy has been its isolation and later products." Hopkins then launched into his habitual explanations and excuses for this oversight. He then turned to the synthesis, expressed confidence in the good faith of his coworkers who performed and reported it, and attributed it, of all things, to coincidence. However, there was not one word about my candid personal communications.

Nevertheless I must have written quite a genteel dear-sir-you-cur epistle to Hopkins, for the last letter I ever received from him, dated 23 xi, 29 from the same place as the previous two, but now bearing a telephone number, ran:

Dear Dr. T. Swann Harding:

You shall of course have a copy of the Glutathione paper as soon as the reprints arrive.

You speak so kindly of the way in which the paper was written that your reminder concerning all lack of reference to your own work (with Dr. Cary) on the subject gives me a feeling of shame. The fault was due, in part at least, to a rather

queer failure of memory at the time of writing up the work, because a little earlier I had determined to write and ask what had become of the results which must have cost you so much labour. I put off writing from time to time, chiefly, I think, because I was not quite sure at what address to find you—I meant to try and ascertain it. I really had felt *very* grateful to you and your colleague for the generous way in which you sent me your interim results, and I ought to have made reference to the fact in my paper. Of course I knew nothing of the treatment you had received from the Editor of the J. B. C., and often wondered that you had not published.

The whole question of my publication was complicated by the fact that I was supposed to be on Sabbatical leave from last Xmas! I got on to the Cu_2O separation just before I was due to start, so I stopped in the laboratory till March, when the job was finished; but then was compelled by my arrangements to go off for two months, and could not, during my travels, get the paper written. On my return some of my colleagues had discovered a queer difference between the old preparations and the crystalline material, vis a vis with tissue preparations. This led me to delay writing up the paper, until, at last, hearing that Kendall was busy and (strictly *entre nous,* for Kendall has treated me well in his paper) fearing that he might hear too much from this ..... who handled the new stuff with me in Cambridge, and went home to Rochester in June, I eventually wrote the paper in a hurry, and (*mea culpa!*) did then somehow forget to mention your kindness to me.

Do forgive my apparent lack of generosity.

I am sorry you are lost to laboratory research, but am sure that your new activities will greatly help progress.

Yours very sincerely,

F. Gowland Hopkins.

Forgive also a very hasty letter!

That ended my brush with fame and my contact with a celebrity. Indeed the last sentence of this letter refers to the fact that I had left research chemistry in the Bureau of Dairy Industry, for far better men to take over, and had become Editor of Scientific Publica-

tions for the U. S. Department of Agriculture. Thereafter I devoted my efforts wholly to editing and writing.

Was Hopkins sincere in his endless explanations, excuses and protestations about being overworked? It is beyond me to tell. Yet Hopkins could not possibly have been in doubt about my address, while it was imperative for him to try to establish contact on so important a matter, assuming my mail would be forwarded if necessary. His reference to J. B. C. refers to the fact that no editor of a journal of biological chemistry intended to dignify by publication the results of unknown little shots when these directly contradicted the published findings of the most outstanding biochemist in the world. We could not get into print. Finally, his fear that Kendall might establish certain priority by publishing ahead of him indicates that credit for his work interested him, however much he felt I should forego it and come up smiling. Be that as it may, it now seems to me that this correspondence has some historical significance and should, after twenty years and Hopkins' death, find its way into print.

BOOK REVIEWS

Practical Emulsions. By H. Bennett. Second edition; xvi + 568 pages, including index. Chemical Publishing Co., Inc., 26 Court St., Brooklyn 2, N. Y. Price: $8.50.

The author, who is Technical Director of Glyco Products, has had wide experience in the field of emulsion manufacture and technical emulsions. The second edition of Practical Emulsions presents a considerable amount of practical data and formulas in this field.

Those interested in emulsion production without too much theoretical data will find the books of some value. Little in the way of emulsion theory is included and, consequently, those without formal training in chemistry and physics will find its pages easily read. The formulas are suggestive of technical manuals giving basic formulas which the experimenter can use as a starting point in developing a product. Food, drug and technical emulsions are presented and a number of literature references cited.

L. F. Tice

Useful Drugs—Fourteenth Edition. Issued under the direction and Supervision of the Council on Pharmacy and Chemistry of the American Medical Association. 241 pages incl. index. 1947. J. B. Lippincott Co., Philadelphia, Pa. Price, $2.00.

Useful Drugs is a small handbook designed to serve as a guide to the medical student and medical examiners in the fields of materia medica and therapeutics. The drugs of basic importance are listed alphabetically with concise information concerning each listed in a clear but brief style. The general sequence followed lists the title, important synonyms, chemical formula, properties, incompatibilities, actions and uses. U. S. P. XIII, N. F. VIII and N. N. R. drugs are included, although not all such drugs are described.

This little book has proven useful in the past both to medical and pharmacy students and it undoubtedly will continue to serve in this field. The average student is so overwhelmed by the classic works on pharmacology and their unabridged coverage of drugs that he experiences great difficulty in selecting that material of primary importance in therapeutics. Useful Drugs is most helpful in this connection. The authoritative character of the selection given to it by the supervision of the Council on Pharmacy and Chemistry makes it of particular value. Practitioners of both medicine and pharmacy will find it a useful quick reference.

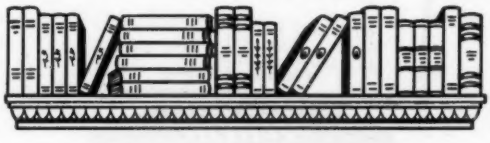
L. F. TICE

Epitome of the Pharmacopoeia of the United States and the National Formulary with Comments. Eighth edition. 238 pages incl. index. 1947. J. B. Lippincott Co., Philadelphia, Pa. Price $2.00.

Like the book "Useful Drugs" this is also published under the supervision of the Council on Pharmacy and Chemistry of the American Medical Association. Since neither the U. S. P. nor the N. F. discuss the uses to which the various drugs are put and do not describe dosage schedules adequately, this data is needed in convenient form by both physician and pharmacist. The "Epitome" has long been known for this purpose. Students of pharmacy in particular will find this book useful in preparing themselves for the state board licensing examinations wherein dosage and use are given great stress in the examination on materia medica.

Its brief but authoritative treatment of this broad subject makes the book very valuable to all pharmacists and students of pharmacy.

L. F. TICE



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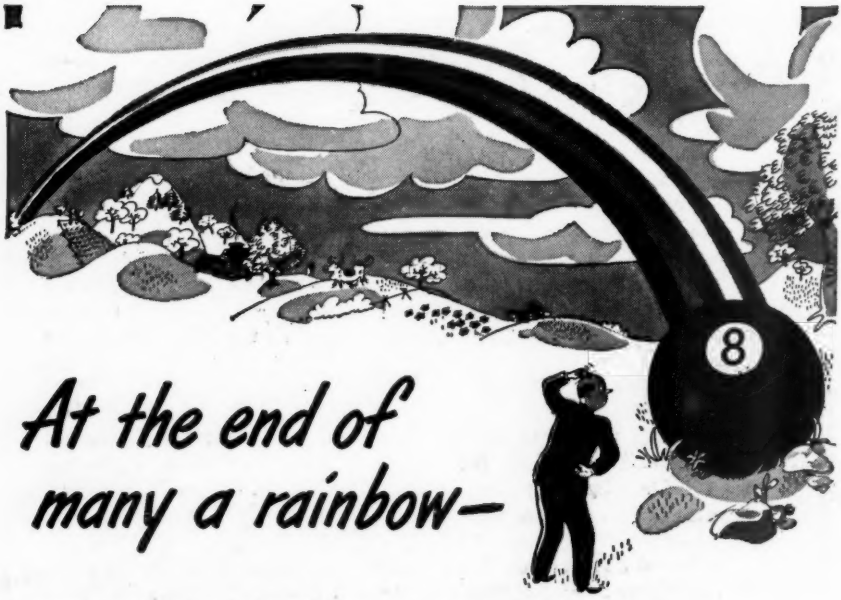

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